REMARKS

Reconsideration is respectfully requested.

Claims 4-9 are pending. Claims 1-3 are cancelled. The inventorship remains unchanged in view of the amendments to the claims. Claim 4 and 9 have been amended. No new matter has been added by way of these amendments. Support for the amendments can be found, for example, in the specification at paragraph 31 and paragraphs 251-285 (Examples 1 & 2).

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Rejections – 35 USC § 112, second paragraph

Claims 4-8 stand rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants have amended claim 4. Claims 5-8 depend upon claim 4.

A.   The Examiner has rejected claim 4, stating that the claim "is directed to method for generating a secondary library; however the method results in generating a tertiary, not secondary, library. Please clarify."

Claim 4 has been amended the preamble to clarify the generated library is a tertiary library. This ground for rejection is therefore moot. Applicants respectfully request that it be withdrawn.

B.   Claim 4d): The Office states, "the phrase 'ranking secondary library' is not clear. Specification does not discuss what kind of 'ranking' is applied to the secondary library (ranking is discussed with respect to 'primary libraries')."

Applicants respectfully traverse this ground for rejection. As discussed with the primary library, a secondary library may be ranked by various methods using many different criteria. For example, the specification states, at paragraphs 32-33:

> "[32]... In some embodiments, lists of sequences that are generated without ranking can then be ranked using techniques as outlined below.
> "[33] In a preferred embodiment, some subset of the primary library is then experimentally generated to form a secondary library. Alternatively, some or all of the primary library members are recombined to form a secondary library, e.g. with new members.

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> Again, this may be done either computationally or experimentally or both." (<u>Emphasis added</u>.)

Thus, any ranking method of primary libraries discussed in the specification will also apply to ranking a secondary library. One of ordinary skill in the art will understand how to rank a secondary library based upon the desired property of the scaffold protein variants.

C.   Claim 4d): The Office states:

> Further, claim 4d is unclear with respect to 'eliminating at least one unfavorable sequence from secondary library'. Specification [sic] does not discuss what are criteria for 'unfavorable' sequences and thus it is not clear what is encompassed by this method step.

Claim 4 has been amended to read, "unfavorably ranked." An 'unfavorably ranked sequence' is well understood by one of ordinary skill in the art. As stated in the previous section, methods of ranking libraries are disclosed in the specification. This amendment merely clarifies what was already implicit in the claim.

These grounds for rejection are therefore moot. Applicants respectfully request that these grounds for rejection be withdrawn.

Claim Rejections – 35 USC § 101/112, first paragraph

Claims 4-9 stand rejected under 35 USC 101 as allegedly lacking support for either a specific asserted utility or a well-established utility. The Examiner has deferred this rejection until the next Applicant's response.

Amended claim 4 is directed to a method for generating tertiary libraries of scaffold protein variants. These tertiary libraries will contain an increased percentage of variants with desired properties relative to a library of random variants. Given that the number of possible variants increase at 20^x-1 for random variants (19 for one position, 399 for two positions, 7,999 for three positions, 159,999 for four positions, 3,199,999 for five positions, etc.,) it rapidly becomes impossible to test all possible protein variants for almost all proteins of therapeutic interest. The ability to test a library of variant proteins with an increased percentage of useful properties is a specific utility that meets the requirements of 35 USC § 101/112, first paragraph.

Claim 9 is directed to a method for generating secondary libraries of scaffold protein variants. These secondary libraries will contain an increased percentage of variants with desired properties relative to a library of random variants. The ability to test a library of variant proteins with an increased percentage of useful properties is a specific utility that meets the requirements of 35 USC § 101/112, first paragraph.

Applicants respectfully submit that claims 4 and 9, as amended, are in condition for allowance. Claims 5-8 depended from claim 4 and are thus allowable for at least the same reasons.

Claim Rejections – 35 USC § 103(a)

Claims 4-9 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Topham (J. Mol. Biol., 1993).

The Cited Reference

Topham teaches a method of modeling an unknown structure from a known sequence using conformationally constrained environment-dependent amino acid residue substitution tables. Topham created the environment-dependent tables from a wider database of all known protein structures and not just members of the protein family. See page 194, left column, bottom bridging to right column, top. Topham address the problem of generating a three-dimensional model for **known** protein sequences of **unknown** three-dimensional structure. For example, Topham states:

> in order to model variable regions it is frequently necessary to select protein fragments from a wider database of all known protein structures, and not just members of the same family.
> Topham page 194, bottom left column to top right column.

Topham never actually generates a library of novel sequences, and thus does not generate a secondary or tertiary library with novel sequences.

As stated in the conclusion, "[i]n this study we have described the calculation of environment-specific amino acid residue substitution tables from a structural alignment database of 33 protein families. Substitutions are scored only when the main-chain conformation of the substituting residue is conserved. This avoids problems associated with the intolerance of certain residues to particular main chain conformations in the prediction of tertiary templates of sequence variation a defined positions within protein folds." See page 217, left column, bottom. In the last paragraph of the paper, Topham states, "[t]here is a growing consensus view that, given the present number of known protein structures, there is no general and simple way to successfully apply database search methods to modeling all loops of unknown structure." Topham is thus trying to predict a structure for a known sequence but unknown structure, not generate a novel sequence from a known sequence.

Worth noting is that in Topham, the terms "substitution" and "template" have a different meaning than similar terms used by Applicants. Specifically, "substitution" as used by Topham

refers to the evolutionary differences at an amino acid position between naturally occurring sequences of a protein family. The information gathered from the various "substitutions" was used to predict the three-dimensional folding of amino acid sequences. Constructing a "template" as used by Topham is building a computer model of an amino acid sequence, not the physical synthesis of an amino acid sequence and certainly not the physical synthesis of a novel amino acid sequence. For example, templates of two β-hairpin families where constructed from single residues at each loop position. See Topham, page 207, bottom left column to top right column.

Claim 4

Topham does not teach or suggest multiple limitations of claim 4.

First, Topham does not teach "a tertiary library of scaffold protein variants." Instead, Topham teaches only known protein sequences. The "substitutions" discussed by Topham refers only to evolutionary differences in families, not tertiary libraries of scaffold protein variants.

Second, Topham fails teach or suggest creating either a secondary or tertiary library of protein sequences "wherein at least one of said secondary sequences is different from said primary sequences." Instead, Topham teaches only known protein sequences with unknown three dimensional structures. None of the sequences described by Topham's secondary and tertiary library are different from the primary sequences considered by Topham. As such, Topham fails to meet this claim limitation.

Third, as admitted by the Examiner, Topham "does not teach synthesizing protein variants form the obtained library of protein variants." The Examiner states, without support, that it would have been obvious to make the claimed variants. To the extent that the Examiner is making Official Notice, Applicants respectfully invite the Examiner to cite a specific reference supporting this position. In the absence of such Official reference, Topher fails to teach all claim limitations, and as such, does not meet this claim limitation.

As such, Topham fails to anticipate claim 4, and those that depend therefrom.

Claim 9

Likewise, Tophan does not teach or suggest every limitation of claim 9.

First, Topham does not teach or suggest "a secondary library of scaffold protein variants," as required by claim 9. Rather, the substitutions taught by Topham are known protein sequences. Moreover, Topham does not teach or suggest creating a secondary library of protein sequences "wherein at least one of said secondary sequences is different from said primary sequences." As above, Topham teaches only known protein sequences with unknown

three dimensional structures. None of the sequences described by Topham's secondary and tertiary library are different from the primary sequences considered by Topham. As such, Topham fails to meet this claim limitation.

As such, Topham fails to anticipate claim 9.

Applicants respectfully request that these grounds for rejection be withdrawn.

Double Patenting

Claims 4-9 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-8 of US 6,403,312 ('312 patent) in view of admitted prior art.

Applicants have attached a terminal disclaimer to overcome this rejection. Applicant also confirms that the instant application and US 6,403,312 are assigned to the same assignee.

Conclusion

In light of the above amendments and remarks, Applicant believes that this case is now in condition for allowance. Early notification is respectfully requested. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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Dated: _October 12, 2005_   By: _____

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